The Interactive Effect of Physical Activity and APOE-ε4 on Cognitive Function in Older Adults

By

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Statement of Sources

I declare that this report is my own original work and that contributions of others have been duly acknowledged.

Signed:

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Abstract

The purpose of this study was to examine the relationship between physical activity (PA) and the APOE-ε4 on cognitive functioning in cognitively normal older adults. Two hundred participants (mean age = 64.35 years old, male *N* = 61, female *N* = 139) estimated their average PA, underwent genetic testing, and completed a battery of neurocognitive tests assessing executive functioning, long-term memory, learning, and working memory. A cross-sectional between subjects 2 (APOE-ε4 carrier status: carrier, non-carrier) x 2 (Physical activity: low, high) ANCOVA (age as covariate) was run for each cognitive test. Results revealed no significant main effects or significant interactions between PA and APOE-ε4 carrier status across any cognitive domains. These results were contrary to the hypotheses. It was concluded that the protective effect of PA, and the risk effect of APOE-ε4 that is present in cases of dementia may not have an effect on non-pathological cognitive decline. Future large-scale research is required to determine whether this is a true effect, or due to methodological limitations. Future research may benefit from the use of an objective measure of PA, inclusion of a measure of global cognitive functioning, and the use of a PA intervention or longitudinal design.

Cognitive decline is a natural part of the ageing process (Deary et al., 2009). Previous literature has identified potential risk factors and protective factors of both pathological and non-pathological cognitive functioning. These factors can be environmental or genetic. The most researched environmental protective factor is physical activity (PA), and the most researched genetic risk factor is presence of the Apolipoprotein E ε4 allele (Cedazo-Minguez, 2007; Sofi et al., 2010). There is a lack of consistency in research regarding the gene environment interaction of cognitive decline (Luck et al., 2014). Further, previous literature has assessed global cognition rather than domain specific cognition (Rovio et al., 2005, Yang et al., 2014). Thus, the aim of this paper is to provide insight on the interaction between low and high PA on carriers and non-carriers of APOE-ε4 on four domains of cognitive functioning; executive functioning (EF), long-term memory (LTM), learning, and working memory (WM).

Cognitive Decline and Ageing

Age-associated cognitive decline generally begins in early adulthood, with noticeable deficits typically occurring from late mid-life onwards (50-60 years old; Salthouse, 2009). The United Nations (2015) predict that by 2050, the number of people aged over 60 years old will have tripled globally since 2000. Thus, as life expectancy increases and the human population continues to age, the prevalence of age-associated cognitive decline (non-pathological cognitive decline) and neurodegenerative dementias (pathological cognitive decline) continues to increase (Brown et al., 2017; Murman, 2015). In 2016 in Australia, the annual cost of cognitive decline including dementias equated to $14.25 billion (such as cost of hospitalisation, pharmaceuticals, and GP visits; Brown, Hansnata, & Anh La, 2017). These figures demonstrate that age-associated cognitive decline is an immediate ever-growing problem. Brayne et al. (2007, p.233) state that due to the non-pathological nature of age-associated cognitive decline it is largely ignored, so much so that he referred to it as ‘the elephant in the room’.

Despite the growing prevalence and cost of cognitive decline, there is a lack of research regarding intervention, diagnosis, treatment, protective factors, and established causal risk factors of cognitive decline (Luck et al., 2014). Before examining the relationship between risk factors, protective factors, and cognitive decline, it is important to identify the facets of cognition that are most affected by ageing. In doing so, the identification of effective domain-specific prevention strategies can be derived.

Cognitive Processes and Ageing

According to Murman (2015), cognitive abilities can be divided into those that are more prone to age-related decline (fluid abilities) and those that remain somewhat unaffected (crystallised abilities). Fluid abilities include the effective manipulation and transformation of information that require complex cognitive processing at the time of assessment. Fluid abilities include EF and WM. Executive functions are a set of cognitive process that encompass the ability to self-regulate behaviour and achieve goals (Salthouse, Atkinson, & Berish, 2003). These processes involve inhibition, visual and verbal attention, task-switching, and cognitive flexibility (Salthouse et al., 2003). Working memory is a fluid ability that refers to the capacity to temporarily hold and manipulate information (Coles & Tomporowski, 2008; Salthouse, 2010).

Conversely, crystallised abilities include knowledge and memories that have accumulated over time, such as general knowledge, semantic memory, and vocabulary. This includes LTM and learning. Long-term memory is a crystallised ability that involves the consolidation and retrieval of information that occurred in the past (Salthouse, 2010). These memories can be consciously available, such as the ability to recall facts, or procedural, such has how to write, walk, and drive (Coles & Tomporowski, 2008). Learning refers to the process of either acquiring new information or modifying existing information (Coles & Tomporowski, 2008).

Cross-sectional research suggests that crystallised abilities increase up and into adulthood, only beginning to decrease in late adulthood (approximately 80 years old). Conversely, fluid abilities

begin to decline in mid-adulthood and the pace of decline increases as age increases (Deary et al., 2009; Harada, Natelson Love, & Triebel, 2013). Whilst previous literature has identified declines in general cognitive ability, the differential determinants of cognitive decline in individuals are not fully understood (Etiner et al., 2015). It has been suggested that lifestyle factors and genetic factors may protect against, or increase risk of cognitive decline in older adults (Lindsay et al., 2002).

Cognitive Reserve Hypothesis

Cognitive reserve (CR) refers the brain's resistance to neuropathological damage and cognitive decline (Scarmeas et al., 2003). CR hypothesis suggests that there are individual differences in the progression of age-associated cognitive decline (Scarmeas et al., 2003). The factors that determine the differences in age-associated cognitive decline amongst individuals are not yet fully understood (Deary et al., 2009). However, some identified factors contributing to a large CR include involvement in higher education, above average estimated intelligence quotient, high occupational attainment, and regular engagement in leisure time activities such as PA (Tucker & Stern, 2011). Research suggests that those with greater CR are often less likely to experience accelerated cognitive decline than those with less CR (Tucker & Stern, 2011). Risk factors of cognitive decline can be environmental or genetic (Lim et al., 2014; Sofi et al., 2010). The identification of risk factors allows the synthesis of preventative measures and early interventions aimed at those most susceptible (Anstey & Christensen, 2000; Luck et al., 2014).

Interventions may be aimed toward modifiable risk factors, such as environmental, lifestyle, or cultural behaviours and exposures that increase risk of cognitive decline (Lindsay et al., 2002). However, developing interventions is much harder for non-modifiable risk factors, such as genetic predisposition to disease, as they cannot be easily manipulated (Lindsay et al., 2002).

The primary identified environmental protective factor against cognitive decline is PA, and the primary genetic risk factor for cognitive decline is being a carrier of one or more Apolipoprotein E epsilon 4 alleles, (Cedazo-Minguez, 2007; Wolk & Dickerson, 2010).

Physical Activity and Cognitive Decline

PA increases cerebrovascular integrity, cellular regeneration, neural plasticity, long-term potentiation, neurotrophic changes, and decreases in stress and depression, which may in turn improve cognitive functioning (Chodzko-Zajko & Moore, 1994; Laurin et al., 2001; Praag et al., 1999). To be considered physically active, one should engage in at least 150 minutes of moderate-intensity PA (e.g. walking, cycling) or 75 minutes of vigorous PA (e.g. running, weight-lifting) per week (WHO, 2017). It is estimated that globally, over one quarter of adults are not active enough (WHO, 2017). This finding is particularly pronounced in older adults (Chodzko-Zajko, 2014).

The majority of previous literature assessing protection against cognitive decline has focused on pharmaceutical interventions rather than potential protective environmental interventions such as PA (Laurin et al., 2001). Further, research has focused on the protective effects of PA and cognitive against pathological cognitive decline such as Alzheimer's disease, largely ignoring age-associated declines (Laurin et al., 2001).

A meta-analysis conducted by Sofi et al. (2010) included 15 studies examining the effect of PA on cognitive functioning in cognitively healthy older adults. Results revealed that sedentary individuals were approximately 35% more likely to experience cognitive decline than their highly active peers. A subsequent meta-analysis conducted by Guure et al. (2017) found a similar protective effect of PA on cognitive decline. However, Guure et al.'s findings displayed a much larger protective effect of PA in cases of pathological cognitive decline compared to non-pathological decline.

A meta-analysis conducted by Smith et al. (2010) examined 29 studies (participant N = 2,049) assessing the protective effect of aerobic exercise interventions on cognitive functioning in adults. Trial periods ranged from six weeks to 18 months. Smith et al. found that subjects who engaged in the intervention displayed a modest improvement in attention, processing speed, and EF,

as compared to the control group. The improvements in WM however, were inconsistent (Smith et al., 2010).

Colcombe and Kramer (2003) conducted a meta-analysis on the effectiveness of fitness interventions on EF in sedentary older adults. Findings revealed that EF was greatly improved from pre-test to post-test. These studies suggest that engaging in PA, even when implemented as an intervention in later life can protect various domains of cognitive functioning against cognitive decline, specifically fluid abilities such as WM and EF. However, longitudinal studies are needed to determine whether PA leads to long-term positive changes in cognitive functioning. As PA is a modifiable protective factor against cognitive decline, it may be delivered as an intervention to genetically susceptible populations to reduce risk of rapid age-associated cognitive decline. The most researched genetic risk factor for Alzheimer's disease is being a carrier of the Apolipoprotein ε4 allele (Cedazo-Minguez, 2007).

Apolipoprotein E

Apolipoprotein E (apoE, protein; APOE, gene) is a polymorphic apolipoprotein that is primarily synthesized by astrocytes in the human central nervous system (Liu et al., 2015). The fundamental roles of apoE is to distribute lipids and cholesterol around the blood stream, lipid clearance, cellular recycling, synaptic plasticity, and membrane repair in the brain following injury (Leoni et al., 2010; Liu et al., 2013). The APOE gene has three common allelic variations: epsilon 2 (ε2), epsilon 3 (ε3), and epsilon 4 (ε4), all producing proteins that differ slightly in structure (E2, E3, and E4 respectively; Marioni et al., 2016). As for all genetic inheritance, individuals inherit one allele from each parent, meaning individuals can carry one of six possible genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4; Cedazo-Minguez, 2007). Carrying two alleles that are not the same (e.g. ε3/ε4) is referred to as a heterozygous genotype, a homozygous genotype occurs when both APOE alleles are the same (e.g. ε4/ε4; Etiner et al., 2007).

APOE-ε3 is the most common allelic variation, as it is present in 77-78% of the global population (Cedazo-Minguez, 2007). Research has found no effect of APOE-ε3 on cognitive functioning, as compared to ε2 and ε3 alleles (Cedazo-Minguez, 2007). APOE-ε2 is present in an estimated 7-8% of the global population (Suri et al., 2015). APOE-ε2 has an identified a protective role for non-pathological cognitive decline and lowering risk of developing dementia (Martins et al., 205). APOE-ε2 is also associated with longevity, fewer amyloid β plaques, reduced risk of cerebral amyloid angiopathy, greater cortical thickness, and larger hippocampal volume than ε3 and ε4 carriers (Liu et al., 2013; Suri et al., 2015; Tirabosci et al., 2004).APOE-ε4 is present in an estimated 14-16% of the population (Etiner et al., 2007). APOE-ε4 has been associated with cardiovascular disease, however it is best known as the primary genetic risk factor for developing Alzheimer's disease, accelerated cognitive decline, and earlier onset of age-associated cognitive decline (Hee Kang et al., 2005; Wolk & Dickerson, 2010). The specific mechanism in which APOE-ε4 affects cognitive functioning is not fully understood, however it has been associated with increased amyloid β aggregation and reduced neurite growth as compared to ε2 and ε3 carriers (Mahley, Weisgraber, & Huang, 2006).

Individuals who inherit one or more APOE-ε4 allele (e.g. ε3/ε4) are referred to as APOE-ε4 carriers. Those who do not inherit the APOE-ε4 allele (e.g. ε3/ε2) are referred to as APOE-ε4 non-carriers. The protein APOE-ε4 (apoE 4) produces has the least stable structure, increased misfolding and a slightly different process of lipid binding as compared to those produced by ε3 and ε2 (Mahley, Weisgraber, & Huang, 2008; Mahley et al., 2006). It has been argued that these structural differences may increase neurodegeneration (Mahley et al., 2006; Zhong & Weisgraber, 2009).

Liu et al. (2013) found that non-carriers mean age of clinical onset of Alzheimer's disease occurred at 84 years of age, heterozygous carriers at 76 years of age, and homozygous carriers at 68 years of age. These findings suggest that homozygous carriers are at far greater risk for rapid and

early onset cognitive decline as compared with non-carriers and heterozygous carriers, therefore demonstrating a dose-dependent response.

APOE-ε4 and Cognition

Previous literature has identified APOE-ε4 as the primary genetic risk factor for Alzheimer's disease (Lui et al., 2013). It has also been suggested that APOE-ε4 has a negative effect on age-associated non-pathological decline (Marioni et al., 2016). A cross sectional analysis conducted by Filippini et al. (2011) examined the effects of age and APOE genotype on brain activation. Filippini et al. assessed fMRI activation in an encoding memory task in a sample of healthy adults. Results suggested that ageing was associated with lower activation and cerebral blood flow in APOE-ε4 carriers, compared with non-carriers. Fillipini et al. suggest that the decrease in activation may reflect vulnerability to late life-pathology, cognitive decline, and changes in brain functioning in APOE-ε4 carriers.

Marioni et al. (2016) conducted a meta-analysis on the differential effects of the APOE-ε4 allele on domains of cognitive functioning. Marioni et al.'s analysis consisted of 18,337 participants aged 18 - 94 years old (M = 47 years old, SD = 15 years). Results of a linear regression analysis revealed that APOE-ε4 was associated with lower performance on memory and processing speed tasks in participants aged over 60 years old, compared with non-carriers. Being an APOE-ε4 carrier was associated also with higher scores of verbal fluency and vocabulary (Marioni et al., 2016). Small et al. (2004) conducted a similar study, finding that APOE-ε4 carriers had poorer global cognitive functioning, episodic memory, and EF in older adults than non-carrier, however the effect sizes were trivial.

These finding consistently indicate that with aging, fluid abilities are being affected by APOE-ε4 (WM, EF, and processing speed), whereas crystallised abilities appear to remain somewhat unaffected (verbal fluency and vocabulary; Salthouse, 2010).

It has been suggested that environmental factors such as PA and diet may influence genetic expression (Ordovas, 2007). Therefore, as interventions cannot alter genetic predisposition to disease, the focus must shift to the relationship between gene and environment (Jaenisch & Bird, 2003). As APOE-ε4 is associated with poorer cognitive functioning, and PA is associated with improved cognitive functioning, the interaction between these factors and how they affect cognition may be of interest.

Relationship between Physical Activity and APOE-ε4

Rovio et al. (2005) conducted a longitudinal study investigating interaction of leisure-time activity and APOE-ε4 carrier status on dementia risk. Participants completed a PA questionnaire, two or more leisure-time activities per week was classified as active, and less than two times per week was considered inactive. Cognitive functioning was assessed by the Mini Mental Status Exam (MMSE). Results revealed that the active group had lower odds of developing dementia than the inactive group. Further, the protective effects of PA were more pronounced in APOE-ε4 carriers than non-carriers. However, these findings were not statistically significant following adjustments for age, sex, education, follow-up time, locomotor disorders, vascular disorders, smoking and alcohol consumption (Rovio et al., 2005). Yang et al. (2014) conducted a similar study, examining the interaction between leisure-time activities and APOE-ε4 carrier status on dementia risk. Results revealed that in APOE-ε4 carriers, only high-frequency PA (more than three times per week) showed protective effects on cognition. Conversely, all types of leisure activities showed a protective effect on cognitive decline in non-carriers (Yang et al., 2014).

A limitation of Rovio et al.'s (2005) and Yang et al.'s (2014) findings may be that their cut-off for what is considered physically active may have been too low, thus those considered active were possibly not active enough to gain health benefits. The Office of Disease Prevention and Health Promotion (ODPHP; 2017) state that total weekly PA should equate to 500-1000 METS to produce substantial health benefits in adults. METS refer to the ratio of energy expended during an activity to

the rate of energy expended at rest. An activity such as walking, may be a six MET activity, meaning it expends six times the energy used by the body at rest (ODHP, 2017). Thus, studies assessing the effects of PA may be more likely to find a significant effect if their definition of PA is meeting ODPHP's (2017) guidelines. A further limitation of Rovio et al.'s (2005) and Yang et al.'s (2014) research is the focus on dementias such as Alzheimer's disease, largely ignoring non-pathological cognitive functioning

Schuit et al. (2001) conducted a study assessing the effect of PA on cognitive decline in older adult APOE-ε4 carriers and non-carriers. Schuit et al.'s sample comprised of elderly Dutch men (N = 347, mean age = 74.6 years old) who were tested in 1990 and again in 1993. Cognitive decline was assessed with the MMSE, defining a decline as a three point or more decrease between testing times. PA was categorised as active (more than an hour of PA per day), and inactive (less than one hour of PA per day). Schuit et al. adjusted for age, education, alcohol consumption, smoking status, and baseline cognitive functioning.

The findings of Schuit et al.'s results revealed that the risk of cognitive decline was similar amongst active and inactive APOE-ε4 non-carriers, however, in carriers the risk of cognitive decline was four times greater when they were inactive compared to active. These findings suggest there is a relationship between PA and APOE, and that PA is particularly important in APOE-ε4 carriers. Furthermore, Schuit et al.'s results revealed that inactive carriers were 13.7 times more at risk for cognitive decline than active non-carriers.

Schuit et al.'s (2001) findings facilitate the identification of subgroups that are most at risk for poor cognitive functioning in later life. Further, they suggest that physically inactive APOE-ε4 carriers have the greatest risk of cognitive decline, and physically active non-carriers are least at risk. This finding has important implications for targeting preventive interventions. However, Schuit et al.'s findings are not without limitation. As the sample comprised only of males the results may not generalizable to females. This is of high importance, as sex differences in cognitive decline have

been reported, with females experiencing greater decline than males (Lipnicki et al., 2007). Thus, further research is required with a more representative sample to determine generalisability. A further limitation of Schuit et al.'s research is the use of the MMSE as a test of cognitive functioning. The MMSE is a relatively blunt tool that assesses general cognitive functioning rather than breaking it down into specific domains. Thus, deficits in one area may be overwhelmed by strengths in another area.

Kivipelto et al. (2008) addressed some of these outlined limitations in their a study aimed to assess the interaction between environmental and genetic risk factors of cognitive decline. In this study, 1149 older adults completed the MMSE in 1977, and again in 1998. PA was categorised as 'active' (more than 50 minutes of high intensity activity per week) or 'inactive' (less than 50 minutes per week). Kivipelto et al. found that APOE-ε4 carriers were significantly more likely to experience cognitive decline than non-carriers, regardless of PA level. In APOE-ε4 non-carriers, physical inactivity increased risk of cognitive decline by 1.8, indicating a very small effect. This suggesting that PA protected against cognitive decline in non-carriers. In active participants, APOE-ε4 carriers were 2.3 times more at risk for cognitive decline than non-carriers, indicating a small effect. Kivipelto et al. further found that inactive carriers were 5.5 times more likely to develop cognitive decline than active non-carriers, indicating a moderate effect.

The findings of Kivipelto et al.'s (2008) study suggests that physical inactivity is a greater risk factor for cognitive decline in APOE-ε4 carriers than non-carriers. Kivipelto et al.'s sample was larger and more representative than, Schuit et al.'s (2001), yet similar results were found. However, these findings have small effect sizes questioning psychological significance. Further research has found conflicting results.

A prospective study by Podewils et al. (2005) conducted from 1992-2000 assessed the effect of PA and genotype on dementia risk. The study consisted of 3,375 older adults who completed the MMSE and the Minnesota Leisure Time Activity Questionnaire. Results revealed an inverse

relationship between PA and dementia risk for APOE-ε4 non-carriers (Podewils et al., 2005). However, no relationship was found between PA and dementia risk in APOE-ε4 carriers. Therefore, Podewils et al. concluded that PA only plays a protective role on non-ε4 carriers. Podewils et al. further argued that the effects of PA may be reflecting overall life engagement and social activity, rather than PA itself. Thus, future research is required to examine PA in isolation of potential confounds. An issue with Podewils et al.'s findings is the focus on dementia rather than age-associated cognitive declines. Thus, the finding of a non-significant relationship between APOE-ε4 carriers and PA has only been found in dementia studies, not in non-pathological studies.

Podewils et al.'s (2005) findings are consistent with that of Obisesan et al. (2012), who reported that high PA was associated with better performance on variations of the MMSE in non-carriers of APOE-ε4 aged 60-69 years old. However, Obisesan et al.'s results found that APOE-ε4 carriers and non-carriers aged 70 years and older performed significantly better on the short MMSE when they were physically active compared to inactive. Obisesan et al.'s results revealed that inactive older APOE-ε4 carriers performed worse than active APOE-ε4 carriers and inactive APOE-ε4 non-carriers, with active APOE non-ε4 carriers performing the best. These results suggest that the effect of APOE-ε4 may become more pronounced with age, allowing PA to have a larger modifiable effect in older age (Obisesan et al., 2012). Further, the interaction effect of PA and genotype was far more pronounced in the APOE-ε4 homozygote subgroup in comparison to the heterozygote subgroup (Obisesan et al., 2012), suggesting a dose-dependent effect.

An issue with the studies above is the use of the MMSE or the short MMSE to assess cognitive functioning. Whilst the MMSE is a reliable and valid measure, it is a relatively blunt tool (Tombaugh & McLyntyre, 1992). Tombaugh and McLyntyre (1992) state that the MMSE provides a brief overview of cognitive functioning but should not be used as a diagnostic tool for cognitive impairments. Further, the MMSE provides a global measure of cognitive functioning rather than

domain specific functioning. As highlighted previously, PA and APOE-ε4 have been shown to affect fluid cognitive abilities (WM, EF) more than crystallised abilities (LTM, learning). Thus, further research is required to determine which domains are most affected by genetic susceptibility, are most protected by PA, and which are most affected by the relationship between APOE-ε4 and PA so that effective interventions can be developed and targeted to groups that would benefit most.

In attempt to close this gap, Etiner et al. (2007) conducted a study to determine the effect of APOE genotype and aerobic fitness on domain specific facets of cognitive performance. Etiner et al.'s (2007) sample comprised of 90 cognitively normal older women. Participants completed a graded exercise test (GXT) to determine aerobic fitness. Participants completed an array of cognitive tests including the Rey-Auditory Verbal Learning Test (RAVLT), the Rey-Complex Figure Test (CFT), the Wisconsin Card-Sorting Task (WCST), and the Paced Auditory Serial Addition Task (PASAT). A regression analysis revealed that aerobic fitness was associated with significantly better performance on measures of LTM (RAVLT, RCFT) in APOE-ε4 homozygotes. Etiner et al. (2007) found a non-significant interaction between APOE-ε4 carrier status and aerobic fitness on measures of WM (PASAT) or EF (WCST). These findings are contrary to their hypotheses based on previous literature and theory, such as cognitive reserve hypothesis.

A limitation Etiner et al.'s (2007) study is the small sample size (only eight APOE-ε4 homozygotes included), and the sample being comprised of female subjects only. This small sample threatens statistical power, generalizability, and reliability of findings. Thus, a larger and more representative sample is needed that examines interaction of APOE-ε4 and PA on domain-specific cognitive functioning.

Aim & Hypotheses

Findings of previous literature has looked at the effects on global cognitive functioning, as measured by the MMSE rather than domain-specific cognitive functioning. Further, the focus of previous literature has been on pathological decline, such as Alzheimer's disease rather than age-

associated cognitive decline. The research on age-associated cognitive decline is also both scarce and inconsistent. Therefore, the aim of the current study was to clarify the relationship between PA level and APOE-ε4 carrier status on cognitive performance in the domains of EF, LTM, learning, and WM in cognitively normal older adults. The following hypotheses are proposed:

1. It is hypothesised that individuals who report high levels of PA will perform significantly better on EF and WM tasks, as compared to those who report low PA. The effect of PA on LTM and learning is hypothesised to be non-significant.
2. It is hypothesised that APOE-ε4 carriers will perform significantly worse than non-carriers on measures of EF, learning, LTM and WM.
3. It is hypothesised that low PA APOE-ε4 carriers will perform significantly worse than high PA APOE-ε4 non-carriers on measures of EF, LTM, learning, and WM.

Method

Design

The current study is employs a cross-sectional between groups 2 (APOE-ε4 carrier status: APOE-ε4 carrier, non-ε4 carrier) x 2 (physical activity: low, high) design. The dependent variables (DVs) of the current study are domains of cognitive functioning; EF, LTM, learning, and WM.

Participants

All participants in the present study had previously volunteered to participate in the Tasmanian Healthy Brain Project (THBP; ethics approval number: H11070), who were invited to participate in the current study. The THBP is an ongoing project aimed to examine the effect of education interventions in later life. Participants of the THBP have undergone genetic testing and annual tests of cognitive functioning. Participants of the present study were given the right to withdraw at any time and were not compensated for their time. The exclusion criteria include being aged under 50 years old and having a family history of Alzheimer's disease. 36% of participants were carriers of the APOE-ε4 allele, whilst 64% were non-carriers.

The initial sample comprised of 225 participants, however 25 were excluded due to incompletion of all measures. The final sample comprised of two hundred participants (male $N = 61$, female $N = 139$) aged over 50 years old (mean age = 64.36, $SD = 6.62$ years)

Ethics approval was gained (approval number: H0016623), and all participants provided informed consent (see appendix A, B, and C). All procedures were conducted in accordance with the APS Code of Ethics and Ethical Guidelines.

Materials

Incidental and Planned Exercise Questionnaire for older people (IPEQ-WA): The IPEQ-WA is a 10-item self-report questionnaire that requests participants to recall their estimated PA over the past three months (Delbaere, Hauer & Lord, 2010). The IPEQ-WA was chosen as it assesses PA estimates of participants' usual week of PA (Delbarere et al., 2010). 'Usual week' questionnaires often demonstrate better psychometric properties than a questionnaires assessing past week PA, which is the focus of most PA scales (Doma et al., 2017). Responses are recorded on a Likert scale from 1-7, where 1 indicates physical inactivity, and 7 indicates high PA. The IPEQ-WA has good reliability and validity in geriatric populations (Merom et al., 2014). The IPEQ-WA was administered online via SurveyMonkey and is estimated to take approximately 10 minutes to complete.

The following battery of neurocognitive assessments were undertaken as part of the Tasmanian Healthy Brain Project:

Hospital Anxiety and Depression Scale (HADS): The HADS is a self-assessment questionnaire that detects symptoms of depression and anxiety (Zigmond & Snaith, 1983). The HADS contains 14 items, seven assessing depressive symptoms, seven assessing symptoms of anxiety. Items are scored from 0-3, where a score of 0 indicates low depression or anxiety, and items scored as 3 indicate high depression or anxiety. The HADS is a generally valid and reliable measure in geriatric samples (Helvik et al., 2011), and takes approximately 5 minutes to administer.

Weschler Test of Adult Reading (WTAR): The WTAR is a neurocognitive assessment designed to predict intellectual performance in adults (Weschler, 2001). The WTAR has good reliability and validity (Whitney et al., 2010). When completing the WTAR, the participant is asked to read aloud 50 words of increasing difficulty. Correct pronunciation is given a score of one, incorrect pronunciation is given a score of zero. The results are averaged and co-normed with the Weschler Adult Intelligence Scale (WAIS) to derive as estimated full-scale intelligence quotient (FSIQ), whereby higher scores indicate greater estimated FSIQ. The WTAR takes approximately five minutes to administer.

*Controlled Oral Word Association Test (COWA*T): The COWAT is a reliable assessment of verbal processing and verbal fluency, which are both aspects of EF (Ross et al., 2007). When administering the COWAT, the test administrator presents the participant with three letters (F, A, S). The participant is given 60 seconds to list as many words as they can that starts with the letter presented. All words correctly recited across the trials are summed to obtain a total score, whereby higher scores indicate greater EF. The COWAT takes approximately 5 minutes to administer.

Trail Making Test (TMT): The TMT assesses visual attention and task switching, which are both measures of EF (Christidi et al., 2013). The TMT is administered in two parts (A and B). The current study only examined part B of the TMT. TMT B instructs the participant to connect letters and the numbers in ascending order (A-1-B-2-C-3-D-4 and so on) (Christidi et al., 2013). The TMT is scored by time taken to complete the task, whereby longer time indicates poorer EF. The TMT generally has high reliability and takes approximately 2-5 minutes to administer (Christidi et al., 2013).

Victoria version of the Stroop Colour-Word Test (VST): The VST assesses selective attention and cognitive flexibility, which are both aspects of EF (Stroop, 1935; Spreen & Strauss, 1998). The VST is a 24-item task that involves three stimulus cards being presented sequentially. Stimulus card one contains coloured dots (blue, green, red, or yellow). The participant must as quickly as possibly

name the colour of the dots. Stimulus card two contains common words (such as; when, over, hard) printed in coloured ink. In this task, the participant is prompted to name the colour of the ink of each word as quickly as possible. Stimulus card three contains the names of colours printed in non-corresponding ink colour. In this task, participants must name the colour of the ink of each word, ignoring the word itself. In the current study 'Stroop interference' was recorded, referring to the difference in reaction time between stimulus one and stimulus three (Malek et al., 2013). Larger Stroop interference scores indicated poorer EF. The VST takes approximately five minutes to administer. The VST is a common and valid neurocognitive evaluation often used in geriatric populations and in those suffering dementia (Bayard et al., 2011).

Rey-Auditory Verbal Learning Test (RAVLT): The RAVLT assesses verbal learning and LTM via examining the participants' ability to store, encode, combine, and recover verbal information (Fard et al., 2016). The RAVLT consists of 15 words which are read to the participant. The participant must then recite all the words they can remember from the list. This is repeated for five trials. To assess verbal learning, the increase of scores from trial one to five is recorded. Larger increase indicates stronger learning. To assess LTM the experimenter reads a second list of 15 words to the participant, this is referred to as the 'distractor list'; aiming to remove items from the first list from the participants' WM. Once the participant has recalled as many words as they can from the distractor list, they must recall as many words as they can from the initial list, without this list being presented again. The aim of this procedure is to assess how many words from the initial list have been consolidated to LTM, where higher scores indicate greater LTM for verbal information. The RAVLT takes approximately 15 minutes to administer.

Rey-Complex Figure Test (RCFT): The RCFT assesses non-verbal LTM (Meyers & Meyers, 1995). The RCFT requires a participant to view a complex figure stimulus card, and copy the image onto a sheet of paper. Three minutes later, the participant is prompted to draw the image entirely from memory. Thirty minutes later, the participant is asked once again to draw the image entirely

from memory. Each drawing is scored for the accurate placement of 18 design elements of the complex figure. Higher scores of the RCFT indicate greater LTM capacity for non-verbal information. The RCFT takes approximately 45 minutes to administer (Meyers & Meyers, 1995).

The Digit Span Test (DSP): The DSP is a subtest of the 3rd edition of the Weschler Adult Intelligence Scale (WAIS-III; Weschler, 1997). The DSP assesses working memory capacity. The administrator reads aloud a sequence of numbers that the participant must recall. If the participant recalls the list correctly, they are given a longer list. The maximum amount of numbers the participant can recall over two trials is recorded (Weschler, 1997). Higher scores indicate greater WM capacity. The DSP takes approximately 5 minutes to administer.

Letter-Number-Sequencing (LNS): The LNS task is part of the WAIS-III (Weschler, 1997). The LNS primarily assesses WM. The administrator reads aloud a random sequence of letters and numbers (e.g. J, 9, X, 3). The participant must recall the letters in alphabetical order and the numbers in ascending order (e.g. 3, 9, J, X). Higher scores indicate greater WM capacity. The LNS takes approximately 5 minutes to administer.

Procedure

Participants of the Tasmanian Healthy Brain Project (THBP) that had completed annual cognitive assessments and had previously had genetic data extractions were invited to participate in this study (N = 344). Participant were informed of the current study through email and postal mailout. The email contained a link redirecting them to SurveyMonkey where they were provided with an information sheet (see appendix A), a consent form (see appendix B), and the IPEQ-WA (see appendix C). Participants who requested a hard copy questionnaire were sent the written invitation, information sheet, consent form, IPEQ-WA, and postage-paid envelope that could then be mailed back to the University of Tasmania upon completion. Participants were requested to release their de-identified cognitive and genetic data as part of the consent process.

In order to maintain the confidentiality clause which was part of the THBP original ethics approval, participant details were de-identified prior to release to the current study. Completed surveys were initially received by the project manager of the THBP (Dr Kim Stuart), who removed identifying information (i.e. names as provided during the consent process), and replaced them with an alphanumeric code for each participant. This master code is only available to the project manager of THBP. Genetic data was extracted via saliva samples following Donohoe et al.'s method (1999). Cognitive data and genetic data was extracted from the THBP database and released to the current study, with the alphanumeric code attached to allow the PA results and cognitive and genetic data to be combined. To ensure security of collected data, hardcopies were kept in a lock safe drawer and electronic data was kept in a password protected Excel file.

Data Screening and Analysis

Participants were grouped by genotype (APOE-ε4 carrier, APOE-ε4 non-carrier) and by PA level (low, high). Exercises noted in the IPEQ-WA were calculated as metabolic equivalents (METS) following Ainsworth et al.'s (2011) compendium. Total weekly PA in the range of 500-1,000 METS is estimated to produce health benefits for adults (ODPHP, 2017). As people are known to inflate responses regarding self-reported PA, per social desirability bias (Adams et al., 2005), high PA was defined as more than 1000 METS per week, and low PA was defined as less than 1000 METS per week.

SPSS version 24 was used to conduct all analyses. Chi Square tests of independence were run to determine whether there were any significant differences in frequencies APOE-ε4 carriers and non-carriers according to different demographic information (sex, control and experimental condition at the THBP and low and high PA status). Independent samples t-tests were run to determine whether there were any significant differences between APOE-ε4 carriers and non-carriers in education, age, estimated FSIQ, Body Mass Index (BMI), and the anxiety and depression subscales of the HADS.

Tests of normality and skewness indicated that in all measures of cognitive functioning, the distribution deviated from normal. Logarithmic and square root transformations were performed to control for skew. As ANOVAs are robust against breaches of normality (Field, 2009) and the transformations did not significantly alter the results, the untransformed data was used in the final analysis. Outliers were present; however, no outliers were more than two standard deviations from the mean, thus they were not removed or transformed in order to maintain power with larger samples (Field, 2009).

Correlations were run to assess the relationship between age and cognitive functioning, as previous literature has suggested that age-associated cognitive decline is far more pronounced in elderly samples (75 years and older) as compared to older adults (65 years and older) (Obisesan et al., 2012). Results revealed that as age increased, performance in some measures of EF (TMT) LTM (RAVLT, RCFT), learning (RAVLT), and WM (LNS) were significantly affected.

Table 1. *Correlations between Age and Cognitive Functioning*

Cognitive Function	Measure	Correlation (*r*) with Age
EF	COWAT	-.088
	TMT B	.379**
	VST inference	.212**
LTM	RAVLT total	-.325**
	RCFT delayed	-.317**
WM	DSP	-.098
	LNS	-.268**

Note: * significant at $\alpha = .05$, ** significant at $\alpha = .01$

Due to the significance of the relationship between age and cognitive functioning, age was included as a covariate. A series of 2 (APOE-ε4 carrier status: carrier, non-carrier) x 2 (Physical activity level: low, high) factorial ANCOVAs were run to assess each neurocognitive assessment. EF was assessed by the TMT, VST, and COWAT. LTM was assessed by the RAVLT and RCFT, and WM was assessed by the DSP and LNS. A 2 (APOE-ε4 carrier status: carrier, non-carrier) x 2 (Physical activity level: low, high) repeated measures ANCOVA was run to assess the differences between groups of the RAVLT learning curve from trial one to trial five to assess learning.

Allelic frequencies were examined using the Hardy-Weinberg Equilibrium chi-square analysis (Emigh, 1980). The analysis revealed no significant differences in observed and expected frequencies (Eisenberg, Kuzawa, & Hayes, 2010) of APOE alleles, $\chi 2$ (5) = 1.90, p = .820 (see Table 2). This suggests the current sample is representative of world allelic frequencies.

Table 2. *Apolipoprotein E Allelic Frequencies: Estimated vs. Observed*

	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4
Worldwide proportion estimate (%)	.1	11.6	2.2	60.1	23.2	2.2
Sample proportion (%)	0.0	9.5	3.5	54.5	28.5	4.0

Results

The demographic data for the final sample is provided in Table 3. As demonstrated, there were no significant differences between APOE-ε4 carriers and non-carriers for age, sex, estimated FSIQ, HADS anxiety and depression scores, higher education, physical activity, body mass index (BMI), or placement in the THBP control or experimental education condition. Significantly more *APOE*-ε4 non-carriers had completed grade 12 than carriers. However, education was not considered as a covariate for this study as there were no significant differences in estimated FSIQ as measured

by the WTAR between genotype groups, and all participants had completed multiple units at the University of Tasmania.

Table 3. *Demographic Information between APOE-ε4 Carriers and Non-carriers*

	Non-Carrier *N* = 128	Carrier *N* = 72	t-test/χ2, (*df*)	*p*
Education (years)				
< Grade 12	11.38 (.90)	11.19 (1.08)	*t* (126) = 1.25	.212
Further education	5.37 (2.71)	4.49 (2.50)	*t* (195) = 2.25	.026
Age (years)	63.88 (6.58)	64.82 (6.12)	*t* (198) = -.98	.328
Gender				
Male N (%)	43 (33.6%)	18 (25.0%)	χ2 (1) = 1.61	.205
Female N (%)	85 (61.2%)	54 (75.0%)		
THBS Group N (%)				
Experimental	103 (80.5%)	55 (76.4%)	χ2 (1) = .46	.497
Control	25 (19.5%)	17 (23.6%)		
Physical Activity				
High N (%)	97 (75.8%)	54 (75.5%)	χ2 (1) = .015	.902
Low N (%)	31 (24.2%)	18 (25.0%)		
FSIQ M (SD)	44.73 (4.52)	43.54 (5.60)	*t* (198) = 1.64	.102
BMI M (SD)	26.69 (5.52)	27.97 (14.17)	*t* (196) = -.91	.362
Anxiety M (SD)	4.41 (3.32)	4.82 (3.06)	*t* (198) = -.85	.395
Depression M (SD)	1.96 (2.25)	2.26 (2.46)	*t* (198) = -.88	.378

Note: * = significant difference between carriers and non-carriers at α = .05

THBS: the Tasmanian Healthy Brain Project, FSIQ: full-scale intelligence quotient estimate, BMI: body mass index

Results of the ANCOVAs revealed no significant main effects of genotype on the battery of neurocognitive tests used (see Table 4 for descriptive statistics stratified by PA level, see Table 5 for

descriptive statistics stratified by genotype, see Table 6 for all ANCOVA inferential statistics, see table 7 for all descriptive statistics stratified by genotype and PA level).

Table 4. *Means and Standard Deviation of the Main Effect PA Level on a Battery of Neurocognitive Tests*

		Low PA		High PA	
		M	*SD*	*M*	*SD*
EF	COWAT	51.49	9.73	52.17	12.03
	TMT B	56.94	20.11	55.43	23.65
	Stroop Interference	1.81	0.35	1.84	9.48
LTM	RAVLT total	51.09	8.91	53.22	10.29
	RCFT delayed	28.30	6.10	28.75	5.91
WM	DSP	18.83	3.72	18.85	3.95
	LNS	11.75	2.44	11.92	2.39

Table 5. *Means and Standard Deviation of the Main Effect of APOE-ε4 Carrier Status on a Battery of Neurocognitive Tests*

		Non-Carrier		Carrier	
		M	*SD*	*M*	*SD*
EF	COWAT	52.56	10.54	51.31	11.46
	TMT B	55.30	23.57	56.16	24.93
	Stroop Interference	1.80	.35	1.90	.42
LTM	RAVLT total	52.79	9.03	51.78	10.29
	RCFT delayed	28.41	5.87	29.31	6.15
WM	DSP	18.87	3.80	18.79	3.89
	LNS	11.89	2.40	11.89	2.40

Table 6. *ANCOVA Results for the Interaction between APOE- ε4 Carrier Status and Physical Activity on a Battery of Neurocognitive Assessments.*

Cognitive Function	Variable	*df* within, error	*F*	*p*	*d*
Long-term memory and Learning	**RAVLT Total**				
	APOE- ε4 Carrier Status	1, 195	0.00	.969	.11
	Physical Activity Level	1, 195	0.99	.321	.20
	APOE-ε4 * PA	1, 195	0.37	.542	.21
	RCFT Delayed				
	APOE-ε4 Carrier Status	1, 195	3.77	.054	.15
	Physical Activity Level	1, 195	0.00	.991	.04
	APOE-ε4 * PA	1, 195	2.12	.147	$\eta\rho^2$ = .011
Working Memory	**DSP**				
	APOE-ε4 Carrier Status	1, 195	0.39	.533	.02
	Physical Activity Level	1, 195	0.42	.517	.05
	APOE-ε4 * PA	1, 195	1.64	.202	$\eta\rho^2$ = .008
	LNS				
	APOE-ε4 Carrier Status	1, 195	0.00	.984	.09
	Physical Activity Level	1, 195	0.13	.715	.02
	APOE-ε4 * PA	1, 195	0.43	.514	$\eta\rho^2$ = .002
Executive Functioning	**COWAT**				
	APOE-ε4 Carrier Status	1, 195	0.01	.940	.15
	Physical Activity Level	1, 195	0.27	.608	.03
	APOE-ε4 * PA	1, 195	1.30	.255	$\eta\rho^2$ = .007
	TMT B				
	APOE-ε4 Carrier Status	1, 194	0.09	.766	.01
	Physical Activity Level	1, 194	0.03	.855	.00
	APOE-ε4 * PA	1, 194	0.67	.414	$\eta\rho^2$ = .003
	Stroop Interference				
	APOE-ε4 Carrier Status	1, 194	2.41	.122	.01
	Physical Activity Level	1, 194	.25	.619	.08
	APOE-ε4 * PA	1, 194	.08	.076	$\eta\rho^2$ = .000

Table 7. *Descriptive Statistics for Cognitive Function of APOEε4 Carriers and Non-carriers, Stratified by Physical Activity Level*

	Low PA				High PA			
	Non-Carrier		Carrier		Non-Carrier		Carrier	
	N = 31		*N* = 18		*N* = 97		*N* = 54	
	M (SD)	95% CI	*M (SD)*	95% CI	*M (SD)*	95% CI	*M (SD)*	95% CI
COWAT	51.68 (7.84)	[47.82, 55.54]	53.61 (11.27)	[48.55, 58.68]	52.85 (11.29)	[50.66, 55.03]	50.54 (11.53)	[47.61, 53.46]
TMT B	53.40 (17.61)	[44.84, 61.95]	59.36 (23.72)	[48.13, 70.58]	55.91 (25.24)	[51.05, 60.77]	55.10 (25.45)	[48.61, 61.58]
VST I	1.76 (.34)	[1.63, 1.89]	1.89 (.38)	[1.71, 2.06]	1.81 (.35)	[1.73, 1.88]	1.90 (.44)	[1.80, 2.00]
RAVLT T	50.94 (8.32)	[47.57, 54.30]	51.22 (10.53)	[46.80, 55.64]	53.38 (9.20)	[51.48, 55.29]	51.96 (10.29)	[49.41, 54.51]
RCFT D	27.36 (6.08)	[25.24, 29.47]	30.31 (4.90)	[27.53, 33.08]	28.75 (5.80)	[27.55, 29.94]	28.97 (6.52)	[27.37, 30.58]
DSP	18.55 (4.12)	[17.19, 19.91]	19.72 (3.20)	[17.94, 21.50]	18.96 (3.70)	[18.19, 19.73]	18.48 (4.07)	[17.45, 19.51]
LNS	11.81 (2.64)	[10.95, 12.66]	11.94 (2.34)	[10.82, 13.07]	11.92 (2.33)	[11.43, 12.40]	11.57 (2.48)	[10.92, 12.22]

Note: COWAT: Controlled Oral Word Association Test, TMT B: Trail Making Test B, VST I: Victoria 24-Stroop task inference, RAVLT T: Rey-Auditory Verbal Learning Test total, RCF DT: Rey-Complex Figure Test delayed, DSP: Digit Span test, LNS: Letter-Number Sequencing.

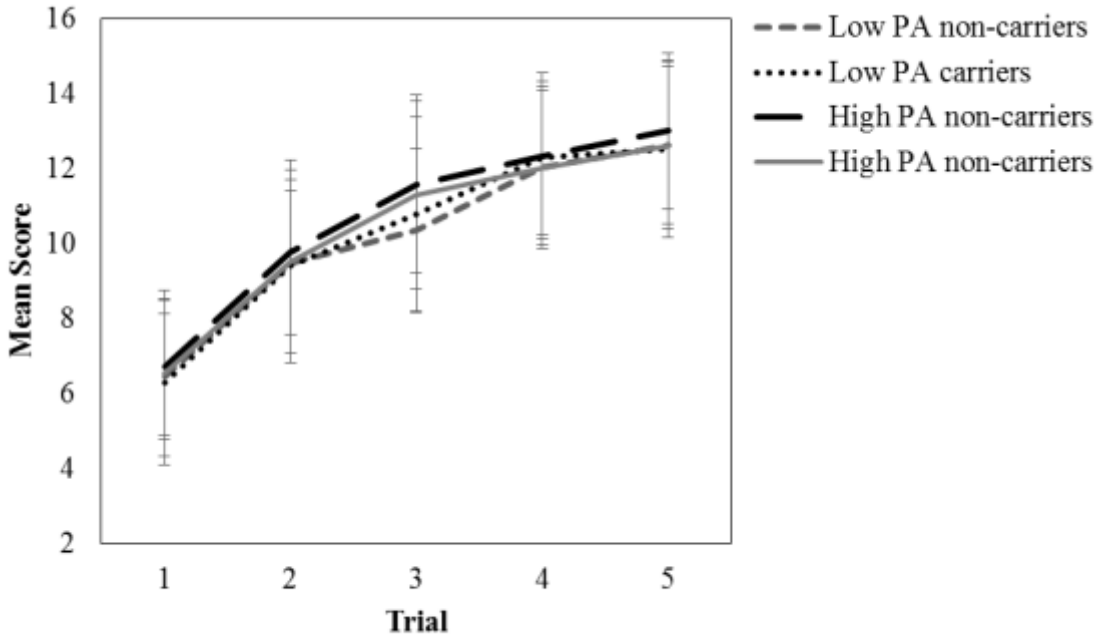
Cognitive functioning was assessed via a series of factorial ANCOVAs and one repeated measures ANCOVA (see Table 5 for all inferential ANCOVA statistics and Table 6 for all descriptive statistics).

2 (APOE-ε4 carrier status: carrier, non-carrier) x 2 (PA level: low, high) ANCOVAs were run to assess the main effects and interactions of APOE-ε4 carrier status and PA level on EF, as measured by the COWAT, TMT B, and VST tasks. Results revealed non-significant main effects or interactions of APOE-ε4 and PA on any measures of EF with trivial effect sizes.

2 (APOE-ε4 carrier status: carrier, non-carrier) x 2 (PA level: low, high) ANCOVAs were run to assess the main effects and interactions of APOE-ε4 carrier status and PA level on LTM. Results revealed non-significant main effects or interactions of APOE-ε4 and PA on any measures of LTM with trivial to small effect sizes.

A 2 (APOE-ε4 carrier status: carrier, non-carrier) x 2 (PA level: low, high) repeated measures ANCOVA was run to assess the learning curve of the RAVLT from trial one (M = 6.58, SD = 1.93) to five (M = 12.79, SD = 2.14). As there were more than two levels of the dependent variable, Mauchley's test of sphericity was violated, $W(9) = .78$, $p = <.001$. Therefore, a greenhouse geisser epsilon correction was applied. Results revealed that overall, performance significantly improved from trial one of the RAVLT to trial five, demonstrating a large effect, $F(3.5, 693) = 565.23$, $p = <.001$, $\eta\rho^2 = .743$. Results revealed a non-significant main effect of PA, $F(3.5, 693) = 2.32$, $p = .064$, $\eta\rho^2 = .012$ with a small effect size. Results revealed a non-significant main effect of APOE-ε4 carrier status on the RAVLT learning curve $F(3.5, 693) = 0.36$, $p = .814$, $\eta\rho^2 = .002$ with a trivial effect size. Further, the results revealed a non-significant interaction between APOE-ε4 carrier status and PA in learning $F(3.5, 693) = .50$, $p = .710$, $\eta\rho^2 = .003$, with trivial effect sizes (see Figure 1).

Figure 1. *Mean Score on the RAVLT from Trial 1-5 of Low and High PA APOE-ε4 Carriers and Non-Carriers*



2 (APOE-ε4 carrier status: carrier, non-carrier) x 2 (PA level: low, high) ANCOVAs were run to assess the main effects and interactions of APOE-ε4 carrier status and PA level on WM, as measured by the DSP and LNS tasks. Results revealed non-significant main effects and interactions of APOE-ε4 and PA on any measures of WM with trivial effect size.

These findings suggest that there is no statistically or psychologically significant effect of APOE-ε4, PA, or the relationship between APOE-ε4 and PA on EF, LTM, learning, or WM.

Yang et al. (2014) found that the interaction APOE-ε4 carrier status and PA on cognitive functioning, until PA was non-significant in high PA versus low PA groups. However, when PA was categorised as ‘vigorous’ versus ‘sedentary, the interaction became significant. Therefore, A 2 (PA: very low, very high) x 2 (APOE-ε4 carrier status: carrier, non-carrier) ANCOVA was run to determine whether vigorous PA (over 2000 METS) and very low PA (less than 500 METS) had

more pronounced effects than high (over 1000 METS) and low (less than 1000 METS) PA. However, results revealed no significant differences, thus the original ANCOVAs were analysed to obtain a larger sample size and maintain statistical power.

Discussion

The majority of previous literature has assessed the relationship of APOE-ε4 and PA on global cognitive functioning (as measured by the MMSE), finding inconsistent results (Kivipelto al., 2008; Podewils et al., 2005). Further, most pre-existing literature that has investigated this interaction has done so in pathological cases rather than age-associated cognitive decline (Luck et al., 2014). The current study is the first to examine the relationship between PA level and APOE-ε4 carrier status on cognitive performance in the domains of EF, LTM, learning, and WM in cognitively healthy male and female older adults. Therefore, whilst the hypotheses were derived from pre-existing theory and literature, the findings of this research are primarily exploratory.

Findings

Results of the present study revealed that the main effect of PA on all domains of cognitive functioning was non-significant. Therefore the hypothesis that the high PA group will perform significantly better than the low PA group on EF and WM tasks, with no significant differences on LTM and learning tasks was only partially supported.

The results of the present study revealed that the main effect of APOE-ε4 was non-significant across all domains of cognitive functioning. Therefore, the hypothesis that ε4 carriers will perform significantly worse than ε4 non-carriers on all measures of cognitive functioning was not supported.

The interaction between APOE-ε4 carrier status and PA level was non-significant on all domains of cognitive functioning. Therefore, the hypothesis that low PA APOE-ε4 carriers will perform significantly worse than high PA APOE-ε4 non-carriers across all measures of cognitive

functioning was not supported. Furthermore, all effect sizes (Cohen's *d* and $\eta\rho^2$) were trivial to very small, revealing no psychologically significant findings.

These results suggest that there is a non-significant effect of PA or of APOE-ε4 on cognitive functioning. These finding further suggest that PA may not affect the expression of APOE-ε4 on cognitive functioning, thus there may not be a gene environment interaction affecting older adults' cognitive functioning across the domains of EF, LTM, learning, or WM.

(In)Consistencies with Previous Literature

Whilst previous literature has typically found an interaction between APOE-ε4 and PA on cognitive functioning, the direction of the relationship has not always been consistent and the effect sizes have often been small (Wisdom, Callahan, & Hawkins, 2011). For example, Podewils et al. (2005) found that PA only improved cognitive performance in APOE-ε4 non-carriers, whereas Schuit et al. (2001) found PA to have a much greater protective effect on APOE-ε4 carriers than non-carriers. Therefore, it is important to emphasise that in this area of research, no pattern of results have been found consistently (Luck et al., 2014).

Results of the current study are somewhat consistent with Etiner et al.'s (2007) research. Etiner et al. found no significant result for heterozygous APOE-ε4 carriers on EF, WM, or LTM. However, Etiner et al. did find that physically fit APOE-ε4 homozygous carriers performed significantly better on LTM tasks than physically unfit APOE-ε4 carriers. Etiner et al.'s sample was small and comprised of females only (N = 90, mean age = 61 years old), thus the findings of the current study may be more generalizable, as a larger and more representative sample was used.

Results of the present study are also somewhat consistent with Rovio et al.'s. (2005) and Kivipelto et al.'s (2012) results, finding non-significant interactions between PA and APOE-ε4 after applying adjustments for age, sex, education, follow-up time, locomotor disorders, vascular disorders, smoking and alcohol consumption on global cognitive decline. Both studies' results revealed PA to have a protective effect on cognition, and APOE-ε4 to have a negative effect on

cognition. Further, both Kivipelto et al. and Rovio et al. found that inactive APOE-ε4 carriers were at greater risk than active carriers, followed by inactive non-carriers, followed by active non-carriers. This pattern of results was not present in the current study (see Table 7). Group means of the current study were very similar, with no group consistently performing better or worse than others amongst multiple tests of cognitive functioning. Thus, susceptibility to environmental manipulations and vulnerability to cognitive decline in certain groups could not be identified.

Results of the current study are inconsistent with Podewils et al. (2005), Yang et al. (2014), and Obisesan et al. (2012) resulting, as they all found a significant interaction between APOE-ε4 and PA on cognitive functioning, with PA having the largest protective effect on non-carriers.

Contributions and Strengths of the Current Study

The majority of previous literature has primarily assessed the effects of APOE-ε4 in relation to patients suffering dementia (Brayne et al., 2007). However, research regarding age-associated cognitive functioning and decline is scarce (Brayne et al., 2007). Studies that have assessed the differences between pathological and non-pathological cognitive decline have identified much larger protective effects of PA and stronger interactions between APOE-ε4 and PA in pathological cases compared to non-pathological cases (Guure et al, 2017). Therefore, a potential explanation for the disparity in results between previous literature and the current study may be the differential effects of APOE-ε4 and PA between pathological and non-pathological cognitive functioning. This finding suggests that APOE-ε4 and PA have no effect on cognitive functioning in healthy older adults, only in pathological cases.

Another potential reason for the disparity of results between both previous studies and the current study is their design and analysis. The current study was a cross-sectional design, meaning that it assessed cognitive functioning at one static time-point. This design may produce different results to those using a longitudinal design, or a pre-test post-test design involving a PA intervention.

A common issue with genetic studies is the low frequency of alleles of interest leading to small or unequal group sizes (Dick et al., 2015). Dick et al. state that candidate gene studies where *N* = less than 1,000 are largely underpowered, thereby increasing the likelihood of revealing a false positive result (type II error) (Dick et al., 2015). This may mean that significant results of previous literature with smaller sample sizes may not reflect true differences in the population. This is also a limitation for the current study, as will be discussed below. These finding may be further emphasised by publication bias leading to significant findings being more likely to be published than non-significant findings (Dick et al., 2015). Therefore, though there is a lack of published non-significant relationships between PA, APOE-ε4, and cognitive decline, does not necessarily mean that these effects have not been found by previous researchers.

Most of the previously outlined literature has assessed cognitive functioning using the MMSE, and has employed varying cut-off points to establish decline. Podewils et al. (2005) classified cognitive decline as a three point or more decrease, whilst Kivipelto et al. (2012) defined a decline as a five point or more decrease on the MMSE. This may be a potential explanation for the disparity of results in both previous literature and in the present study. In attempt to overcome this limitation of previous literature, the current study took a domain-specific approach rather than relying on the MMSE. This approach is far more in depth than the relatively blunt MMSE, as it allows for the potential identification of specific cognitive strengths and weaknesses Tombaugh & McLyntyre, 1992). Domain-specific tests also facilitate the identification of which domains of cognitive functioning may be the most and least affected by APOE-ε4, PA, and the relationship of both (Tombaugh & McLyntyre, 1992). Thus, the testing of cognitive functioning was a major strength for the current study.

The PA questionnaire used in the present study (IPEQ-WA) has been cross-validated with objective measures of PA and was designed to measure PA in geriatric populations (Delbaere et al., 2010). This is considerable of the current study, as what is considered physically active compared to

inactive varies greatly amongst previous studies. The majority of previous literature in this field has assessed participants' past week of PA via self-reported, unstandardized questionnaires that have not been designed or validated for use in geriatric populations (Podewils et al., 2005). A primary problem with this assessment technique is that a participant's past week of PA may not be representative of their normal week (Doma et al., 2017). Furthermore, previous literature has found that not all forms of PA produces health benefits (Watts et al., 2013), with vigorous activities such as weight lifting leading to much greater health benefits than low intensity activities such as walking (Yang et al., 2014). In attempt to overcome the limitations of PA measure found in previous literature, the current study calculated the METS of physical activities listed in the survey and implemented a high cut-off point for what was considered 'active' (ODPHP, 2017). Given that much of the previous literature has included low-intensity PA and has not calculated METS, this disparity in PA classification may account for some discrepancy in the results of previous literature (Podewils et al., 2005). Another limitation of previous literature's PA measure is the reliance on the recall of past PA in a geriatric sample. This is somewhat overcome in the current study by using a questionnaire requesting 'usual week' PA as compared to 'past week' questionnaires, relying less on specific memory and more on estimates (Doma et al., 2017). 6t5

Limitations

One of the primary limitations the current study faces is the methodological design. A cross-sectional approach allows identification of current cognitive functioning, however a longitudinal approach would have permitted detection of differences in trajectories of decline, should they exist. Therefore, groups with the best and poorest current performance can be identified, but the rate of decline, and scope of decline cannot be determined.

Though the sample size of the current study was not particularly small (N = 200), once stratified into four groups, some groups were relatively small (e.g. low PA APOE-ε4 non-carriers N = 18). This led to uneven groups, threatening the robustness of ANCOVAs, and low post-hoc

statistical power (Dick et al., 2015; Field, 2009). This is a common problem in genetic and biomedical science, as allelic frequencies in the general population are low (i.e. APOE-ε4 only present in 15% of the general population), samples often have a low frequency of APOE-ε4 carriers (Dumas-Mallet et al., 2017; Etiner et al., 2015). Thus, larger studies are needed to allow a more robust exploration of this relationship.

A further limitation of the current study is that over two thirds of the sample were categorised as engaging in high PA. Considering that over one quarter of adults are estimated to be physically inactive globally (WHO, 2017), this incidence of high PA versus low PA participants seems atypical. Per social desirability bias, participants are prone to over-inflation of PA estimates (Adams et al., 2005). This means that those categorised as highly physically active may not have truly been. However, the cut-off set for what constitutes as highly active (1000 METS or more) was set at the maximum recommended METS (1000 METS or more) by ODPHP (2017) in attempt to overcome this limitation. This cut off point means that estimates from sedentary participants would have to be extremely inflated to appear as highly active in the current study. Further, when only very high PA (> 2000 METS vs < 500 METS) was compared to very low PA, the results remained non-significant, suggesting bias doesn't fully account for the null findings. Another potential explanation for this stratification of PA level may be due to participation bias (Barreto et al., 2012). Participation bias argues that people who are motivated to volunteer to participate in studies assessing PA are significantly more physically active than those who do not.

Future Research

There is no prevailing pattern of results that clearly defines the relationship between PA, APOE-ε4, and non-pathological cognitive functioning. Therefore, future research is required to clarify these effects and interactions. Future research should aim to investigate the potential differences in the relationship between PA and APOE-ε4 between dementia versus age-associated cognitive decline. This research may be beneficial in understanding the gene environment interaction

of cognitive functioning, and may help determine whether there truly is no effect of PA and APOE-ε4 on non-pathological cognitive functioning.

There are a number of methodological issues that could be addressed in future research in this area. For one, future research should aim to conduct large-scale studies employing interventions or a longitudinal design. Further, as age was a covariate of the current study, and Obisesan et al. (2012) found the effect of PA to impact APOE-ε4 differently at different age intervals, future research may benefit from including age as an independent variable, comparing those aged 60-69 years old to those aged 70 years and older. For a more evenly stratified sample regarding PA, future research should aim to recruit participants from a range of samples, as the participants of the THBP are particularly motivated to participate (Barreto et al., 2012). This may also be achieved by implementing a quota of active versus inactive participants, only closing recruitment when this quota is met. This method may also reduce the large variances in group sizes, leading to a more robust ANOVAs (Field, 2009).

For a more accurate measure of participants' PA, future research should use a self-report questionnaire that has been validated in a geriatric sample (Prince et al., 2008). This used in conjunction with an objective measure of PA such an accelerometer or a measure of aerobic fitness may provide the most reliable results (Prince et al., 2008). Using a measure of life-time PA may also be beneficial to determine whether PA has long-term effects on cognitive functioning (Colcombe & Kramer, 2003).

Dose-dependency suggests that being an APOE-ε4 homozygous carrier significantly increases risk of developing dementia than APOE-ε4 heterozygous carriers (Obiseasan et al., 2012). The current study did not have a large enough sample to warrant breaking down genotype groups from APOE-ε4 carriers and non-carriers to their specific genotypes (e.g. ε4/ε4). Therefore, future research may benefit from further exploring the differences between homozygous APOE-ε4 carriers and heterozygous carriers. Literature has also suggested that the APOE-ε2 allele's protective effects

against dementia and age-associated cognitive decline may overpower the risk factor APOE-ε4 presents (Suri et al., 2013). Thus, future research may benefit by excluding ε2/ε4 carriers from analysis to control for this affect.

Future research should also aim to explore other variables that may interact with PA and APOE-ε4 on cognitive functioning. APOE is not the only gene associated with cognitive decline (Sapkota et al., 2015). It has been found that the combined effect of APOE and BDNF may lead to more pronounced effects on cognition (Sapkota et al., 2015; Ward et al., 2014). Therefore, future research may benefit from examining the gene environment interaction between APOE, BDNF, and PA. Other variables that may be important to consider include diet, social engagement, and education (Smith et al., 2010).

Conclusions

Findings surrounding the potential effects of PA, APOE-ε4, and their interaction on age-associated cognitive decline has been inconsistent and scarce. The research that has been conducted in this field has often comprised of small samples consisting of one gender (Etiner et al., 2007; Schuit et al., 2001), used unstandardized measures of PA that are not validated for geriatric samples (Podewils et al., 2005), and have relied on the use of the MMSE to determine cognitive functioning, ignoring potential domain-specific differences (Tombaugh & McLyntyre, 1992).

The current study aimed to overcome these limitations by examining the interaction of PA and APOE-ε4 across domains of cognitive functioning, assessing PA with a questionnaire valid for a geriatric sample, and accounted for social desirability bias via increasing MET cut-offs. Thus, though this study was not without limitation, it presented with some considerable strength over previous literature. Results of the current study revealed no significant effects or interactions between PA and APOE-ε4 on age-associated cognitive decline across the domains of EF, LTM, learning, and WM, contrary to the hypotheses. From the current research, genetically at risk groups cannot be identified, and groups that may benefit most from interventions also cannot be identified.

The findings of the current study suggest that PA and APOE-ε4 may not effect on age-associated cognitive decline, and this effect may only be present in pathological cases. However, this is not consistent with all literature, thus future research is required. This research would benefit from employing a longitudinal design or a pre-test post-test PA intervention. Further, a large and representative sample, an objective measure of PA would help to determine whether this is a prevailing pattern of results, or due to methodological inconsistencies. Further, future research should examine possible relationships with other variables, such as diet, BDNF, and age, as well as investigating dose-dependency further.

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Appendices

Appendix A: *Ethical Approval*

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HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

31 July 2017

Ms Christine Padgett
C/- University of Tasmania

Sent via email

Dear Ms Padgett

REF NO: H0016623
TITLE: Exploring the Roles of Physical Activity and Genetic Predictors on Cognition in Older Adults

Document	***Version***	***Date***
Low risk Application		13 July 2017
HLAQ Modified for Australia		
Introduction for THBP Newsletter		
Cover letter Padgett		10 July 2017
Email and Mail introduction PA and Gene Study		
Finance and Administration		
Incidental and Planned Exercise Questionnaire		
PICF PA		13 July 2017

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **27 July 2017** to be conducted at the following site(s):

Wicking Dementia Research and Education Centre

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.utas.edu.au/research-admin/research-integrity-and-ethics-unit-rieu/human-ethics/human-research-ethics-review-process/health-and-medical-hrec/managing-your-approved-project

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for four years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 27 July 2018**.** You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 6254.

Yours sincerelv

Jude Vienna-Hallam
Ethics Administration Officer

Appendix B: *Participant Information Sheet*

UNIVERSITY of TASMANIA

PARTICIPANT INFORMATION SHEET
Exploring the Roles of Physical Activity and Genetic Predictors on Cognition in Older Adults

Invitation

We would like to invite you to participate in a research project investigating whether physical activity influences the way genes might impact cognitive function (for example memory and learning). This study is being run as a side-project by researchers in the Tasmanian Healthy Brain Project and researchers at the School of Medicine (Psychology).

The study is being conducted by:

- Dr Christine Padgett, Lecturer in the School of Medicine (Psychology), UTAS
- Associate Professor Mathew Summers, Associate Professor of Neuropsychology and Mental Health, Thompson Institute, USC and Investigator in the Tasmanian Healthy Brain Project, UTAS
- Professor James Vickers, Professor of Pathology, Wicking Centre, UTAS
- Kimberley Stuart, Research Fellow and Project Co-ordinator, The Tasmanian Healthy Brain Project UTAS
- Ruby Marris-Smith, 4th year Honours Student in the School of Medicine (Psychology) UTAS
- Melissa Heather, 4th year Honours Student in the School of Medicine (Psychology) UTAS

1. "What is the purpose of this study?"

There is evidence that some genes might influence cognitive function in later life (for example, memory and learning). However, it is possible that physical activity influences the effect of these genes. Therefore we would like to investigate the relationship between physical activity, genes thought to influence cognition, and cognition in older adults.

2. "Why have I been invited to participate in this study?"

You have been invited to participate in this study because you are currently participating in the Tasmanian Healthy Brain Project.

3. "What does this study involve?"

For this study, you would be asked to complete two short questionnaires; one asking you about past levels of physical activity and the other asking about your current levels of physical activity. These questionnaires can be either completed online or can be mailed to your home, where you can complete and the return in a postage-paid envelope that we will provide. Completing the questionnaires should only take about 10 minutes in total.

We would also ask that we could access the results of the cognitive assessments you have undertaken as part of the Tasmanian Healthy Brain Project, as well as the genetic results from the samples you provided. It is important to note that any data provided by researchers at the Tasmanian Healthy Brain Project would not have your name or any information that could identify who you are. Only Associate Professor Summers or Ms Stuart, who are also researchers

on the Tasmanian Healthy Brain Project, would have your identifying information, and would remove these details and insert an alpha-numeric code in its place before passing on as to the current project.

4. "Are there any possible benefits from participating in this study?"

It is not expected that there will be any specific benefits from participating in this study.

5. "Are there any possible risks from participation in this study?"

We do not foresee any risks associated with participating in this study.

6. "What if I have questions about this research?"

If you would like to discuss anything about this study you are very welcome to contact Dr Christine Padgett on 6430 4946 or email her at Christine.Padgett@utas.edu.au. If you have concerns or complaints about the conduct of this study should contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to quote HREC project number H0016623

Thank you for taking the time to consider this study. If you would like to take part, and have received this via email, please click on the link in this email. This will take you to a consent form and then on to the survey. If you have received this via mail, please complete the enclosed consent form and enclosed questionnaires and return using the postage paid envelope.
This information sheet is for you to keep

Appendix C: *Participant Consent Form:*

CONSENT FORM
Exploring the Roles of Physical Activity and Genetic Predictors on Cognition in Older Adults

1. I have read and understood the information sheet for this project.

2. I understand that I will be asked questions relating to past and present physical activity, and that this survey will take approximately 10-15 minutes to complete.

3. I consent that the Tasmanian Healthy Brain Project can release my data to be included in this study.

4. I understand that there are no foreseen risks associated with this study.

5. I understand that all research data will be securely stored at the University of Tasmania for at least five years following publication of results, and will be destroyed when no longer required.

6. Any questions that I have asked have been answered to my satisfaction.

7. I agree that research data gathered from me for the study may be published provided that I cannot be identified as a participant.

8. I understand that any information I provide will be only used for the purposes of this research.

9. I understand that I may withdraw at any time without any consequences, and that I can request for my data to be removed from the study at any time.

If you have read and understood the information sheet and above points, and wish to be involved in the study, please click 'yes' below and you will be directed to the survey. If you do not wish to be part of this study, please click on the 'No' below and you will be exited from the survey. We thank you for your time.

Name of Participant:_____

Signature:_____
Date:_____